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Clinical Investigative Studies

Paradoxical Emboli From Calf and Pelvic Veins in Cryptogenic Stroke

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ABSTRACT

Purpose. The increased prevalence of patent foramen ovale in patients with cryptogenic strokes suggests the occurrence of paradoxical embolism. The identification of deep venous thromboses (DVTs) in this population would strengthen this hypothesis. The purpose of this study was to image the subdiaphragmatic venous system in a cohort of patients with cryptogenic strokes. **Materials and Methods.** In 37 patients with cryptogenic brain ischemia and interatrial communication, duplex studies of calf, popliteal, and femoral veins, and magnetic resonance imaging venograms of the pelvic veins were performed. **Results.** In 10 patients, DVTs were diagnosed that were considered to be the cause of cryptogenic brain ischemia on probable ($n = 6$) or possible ($n = 4$) bases. In these patients, the median time from stroke to DVT was 3.25 days. In 5 of these 10 patients, DVTs did not involve popliteal and femoral veins, areas thought most important to pulmonary embolism, but instead were isolated to calf or pelvic veins. Although none of these 10 patients had abnormal blood hypercoagulation tests, 8

of the 10 did have clinical conditions suggesting predisposition to developing DVTs, such as concomitant neoplasms or pulmonary embolism. **Conclusions.** Increased evidence for paradoxical embolism may emerge when diagnostic strategies use multiple imaging methods and evaluate a broad extent of the subdiaphragmatic veins.

Key words: Cryptogenic stroke, paradoxical embolism, deep venous thrombosis, patent foramen ovale.

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No cause can be identified in 26% to 40% of all ischemic strokes¹⁻³ and in 64% of patients under age 55.⁴ Such cases have been termed *cryptogenic strokes*. A better understanding of stroke pathophysiology in these patients could be important to improving secondary stroke prevention.

Although a number of different processes likely contribute to cryptogenic stroke, several lines of evidence suggest that paradoxical embolism through a patent foramen ovale (PFO) is one important subgroup. The prevalence of PFOs in patients with cryptogenic strokes is 42% to 73%, significantly higher than controls or patients with strokes of determined origins.⁵⁻⁸ Brain imaging in this population suggests embolic strokes.^{1,9} The rate of stroke increases with larger PFO size; for example, several studies⁹⁻¹⁴ have suggested that in patients with cryptogenic strokes, the sizes of the interatrial shunts are larger than in

patients with strokes of determined origins or in normal controls. The risk for PFO-related stroke is further increased when an atrial septal aneurysm is also present,^{5,15} though the presence of an atrial septal aneurysm may in part be a reflection of larger PFO size.¹⁶

Cryptogenic stroke in the presence of an interatrial shunt is a common clinical scenario, but the fraction of cryptogenic strokes accounted for by paradoxical embolisms remains uncertain because a venous source of embolic material has not been identified. The increased detection of deep venous thromboses (DVTs) in patients with cryptogenic strokes and PFOs might be achieved by using multiple diagnostic modalities and by evaluating all subdiaphragmatic veins. The current study reports the results of combined duplex and magnetic resonance imaging (MRI) evaluation of the subdiaphragmatic venous system in a cohort of 37 patients with cryptogenic brain ischemic events plus right-to-left intracardiac communication.

Patients and Methods

During the service time of 2 physicians (SCC, WSB), a venous system study was performed as part of clinical evaluation in 37 patients with interatrial shunts and cryptogenic brain ischemic events. Events were labeled *cryptogenic* only after the normal evaluation of extracranial and intracranial arteries and echocardiography. Of the 37 patients, 6 were from the University of Texas, Houston (UT), and 31 were from the University of Washington (UW). The mean (\pm SD) age was 54 ± 16 years (range, 22-80 years). There were 25 female and 12 male patients. Arterial studies used Doppler methods in 19 patients, magnetic resonance angiograms in 7, catheter angiograms in 5, and 2 or more of these methods in 6. Echocardiograms were transesophageal in 20 patients and transthoracic in 17 patients. PFOs were present in 35 patients, 5 of whom had concomitant atrial septal aneurysms, while 2 patients had atrial septal defects (ASDs).

Among these 37 patients, the median time from cerebral ischemic event to the first study of the venous system was 8 days. At the time of venous system evaluation, 23 patients were receiving antiplatelet agents, 9 were receiving anticoagulation, 2 were receiving both, 1 was < 24 hours after intravenous tissue plasminogen activator, and 2 were receiving no treatments related to thromboses. There were 22 inpatients and 15 outpatients. Brain ischemia was transient ischemic attacks in 6 patients and strokes in 31.

Venous system evaluation included leg vein duplex and pelvic vein magnetic resonance venography (MRV). Venous duplex exams included the evaluation of the bilat-

eral deep femoral, superficial femoral, and popliteal veins. At UW, duplex exams also included the tibial, saphenous, and peroneal veins.

Pelvic MRV included time-of-flight (TOF) and phase-contrast (PC) imaging using a torso coil at 1.5 T, without the introduction of contrast. The field of view extended from the infrarenal inferior vena cava to the proximal common femoral vein. For TOF images, slices were 3 mm thick with 2-mm skips between slices. For PC images, slices were 5 mm thick with no skips and were in plane with TOF slices.

Pelvic MRV images were reviewed by 2 radiologists specializing in abdominal-pelvic imaging who were blinded to all patient clinical data. The final read for the study was either positive or negative for acute pelvic DVT, on the basis of consensus opinion. MRV was deemed positive for acute DVT when both radiologists identified a 15-mm or longer intravascular decrease in signal intensity on TOF images that contacted the wall of the vein. The intravascular signal decrease on PC images was required to match the TOF abnormality.

A paradoxical embolism was considered to be the cause on a probable basis when 2 criteria were met: (1) DVT was documented < 4 days after or up to 1 week prior to the cerebral ischemic insult, and (2) a PFO or an ASD was demonstrated on echocardiogram. Four days poststroke was chosen in defining probable paradoxical embolism because the incidence of poststroke DVT rises significantly after this time.¹⁷ A paradoxical embolism was considered as being the possible cause of the cryptogenic brain ischemic event when a PFO or an ASD was present, and many features were suggestive of a paradoxical embolism, but the first criterion was not completely met. An acute DVT was excluded from either category if diagnosed ≥ 4 days poststroke in a patient with hemiplegia.

Results

A total of 14 of 37 patients were diagnosed with DVTs. Five of these were in the pelvic veins, including 1 patient from UT, and 9 of these were in the leg veins, including 1 patient from UT. In 4 of these 14 patients, the DVTs were determined to be consequences of strokes because of either hemiplegia, DVTs arising after normal poststroke leg duplex exams, or the chronic appearance of DVTs when imaged early after stroke. In the other 10 of these 14 patients, paradoxical embolisms were determined to be the cause of cryptogenic brain ischemia on probable or possible bases. Note that MRV was not performed in 7 of 37 patients for a number of reasons, including MRI availability, claustrophobia, or the diagnosis of calf DVTs.

Table 1. Ten Patients With Probable or Possible Paradoxical Emboli as Cause of Cryptogenic Brain Ischemic Events (PFO size is noted when available)

Patient	Age/Sex	Clinical Features	Venous Thrombus	Interatrial Shunt	Cryptogenic Cerebral Ischemic Event
Probable cases of paradoxical embolism to the brain					
1	27/M	Sickle cell disease; history PE; moderate hemiparesis with stroke	L EIV DVT extending to L CFV, 3 d poststroke	PFO	ACA cortical stroke
2	68/M	Rectal melanoma; postoperative TIA ^a	R calf DVT found 6 d before, confirmed 1 d after, TIA	PFO	TIA
3	57/M	Thalamic abscess found 12 d prestroke; PE diagnosed 3 d prestroke ^a	L calf DVT, 3 d prestroke	Small PFO and ASA	Multiple, simultaneous cerebral and cerebellar small strokes
4	51/F	Essential thrombocytosis; recent history benign pelvic mass; multiple prior embolic strokes ^a	Bilateral DVT from calf veins to IVC, first diagnosed 5 mo before, confirmed 3 d after, stroke	PFO	Multiple, bilateral small cortical strokes
5	78/M	Stage III rectal adenocarcinoma, with resection 3 mo prestroke ^a	R CIV DVT, 3.5 d post-CVA	PFO	Parietal cortical CVA
6	54/F	4 y of birth control pills; mild hemiparesis with stroke	L saphenous vein DVT extending to popliteal vein, 2 d poststroke	Moderate PFO	Frontal cortical CVA
Possible cases of paradoxical embolism to the brain					
7	78/F	Prior porcine aortic valve replacement ^a	L thigh DVT 10 mo prestroke; R calf chronic DVT 2 mo poststroke	Moderate PFO and ASA	Large PCA stroke
8	57/F	Prior cryptogenic stroke TIA with concurrent PE ^a	L CIV DVT, 7 d post-TIA/PE	PFO	TIA
9	38/M	R knee trauma and R popliteal surgery preceding stroke ^a	Chronic DVT R popliteal vein, first diagnosed 12 mo poststroke	PFO	Basilar artery embolus
10	43/F	Smoker on birth control pills ^a	R peroneal, posterior tibial, and soleal vein DVT, 6 d post-CVA	PFO and ASA	Posterior inferior cerebellar artery territory stroke

PFO = patent foramen ovale, M = male, PE = pulmonary embolus, L = left, EIV = external iliac vein, DVT = deep venous thrombosis, CFV = common femoral vein, ACA = anterior cerebral artery, TIA = transient ischemic attack, R = right, ASA = atrial septal aneurysm, F = female, IVC = inferior vena cava, CIV = common iliac vein, CVA = cerebrovascular accident, PCA = posterior cerebral artery.

a. Indicates no motor deficits with cerebral ischemic event.

Among the 10 patients with possible or probable paradoxical embolisms (Table 1 and Fig 1), the mean age was 55 ± 17 years (range, 27-78 years), and the median time from stroke to DVT diagnosis was 3.25 days. There were 5 female and 5 male patients. At the time of venous system evaluation, 5 were receiving antiplatelet agents, 3 were receiving anticoagulation, 1 was receiving both, and 1 was receiving no treatments related to thrombosis. Note that the DVTs in 5 of 10 patients were restricted to calf or pelvic veins. No blood hypercoagulable tests were abnormal in these 10 patients, including negative results on testing IgG and IgM anticardiolipin antibody in 6 patients, acti-

vated protein C resistance in 5, protein S in 7, protein C in 6, and antithrombin III in 6; lab error, the early initiation of warfarin, and other factors prevented complete testing in some patients. However, hypercoagulable states were suggested in 8 of 10 patients' histories: prior (2) or concurrent (1) pulmonary embolism, prior leg DVT, essential thrombocytosis, rectal adenocarcinoma, melanoma, and smoking while taking birth control pills.

In 3 patients, only TOF imaging was performed; in none of these were images suggestive of possible or probable paradoxical embolisms. In 6 patients, the same field of view was covered by a larger number of thinner MRI

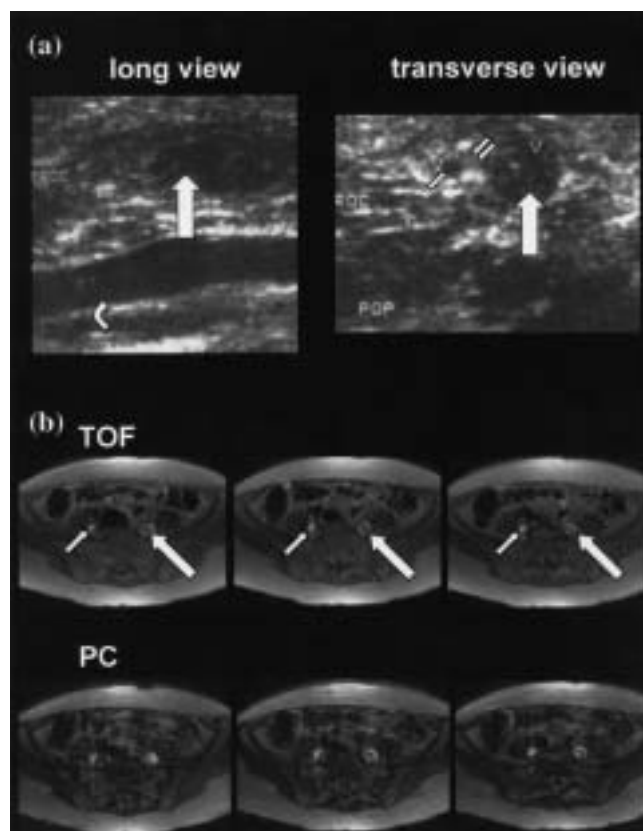


Fig 1. (a) A positive calf vein duplex study in the long view (left) and transverse view (right) from patient 3. One of the paired gastrocnemius veins (large arrow) is dilated, has some soft echogenicities, and did not compress. These features are consistent with an acute deep venous thrombosis (DVT). The other gastrocnemius vein (small arrow) and artery (double arrow) are normal in size, as is the popliteal vein (curved arrow). (b) A positive pelvic magnetic resonance venography scan from patient 8 showing the time-of-flight (TOF) (upper row) and phase-contrast (PC) (lower row) pulse sequences. The left common iliac vein has a site of decreased signal intensity (long arrows) consistent with a DVT. The findings are present on 3 contiguous slices of 5 mm in thickness and are matched on the 2 pulse sequences. In addition, the left common iliac vein is dilated, whereas the right common iliac vein (short arrows) is normal. This patient's leg vein duplex study was normal.

slices because of a technical error. Of these 6 patients, 1 was considered to have a possible, and none a probable, paradoxical embolism.

Discussion

The majority of patients with cryptogenic strokes also have PFOs, suggesting paradoxical embolisms as the basis of the strokes in some patients. However, a venous source of thrombus has infrequently been identified, calling into question whether PFOs are truly relevant to the genesis of strokes.¹⁸ The current study identified 10 pa-

tients with cryptogenic brain ischemia plus right-to-left intracardiac communication in whom DVTs were possibly or probably the origin of paradoxical embolisms. Importantly, half of these 10 DVTs were restricted to calf or pelvic veins; that is, they did not involve popliteal or femoral veins.

The prevalence of DVTs among patients with cryptogenic strokes and interatrial shunts is unclear because most previous studies did not consistently examine all subdiaphragmatic veins or were not restricted to cryptogenic strokes. In studies of stroke patients with PFOs but not restricted to cryptogenic strokes, DVTs were found in 6% of an unspecified subset,¹⁹ 5 of 53 patients (9.5%) with suspected cardioemboli,²⁰ and 19 of 35 patients (54.3%) with cerebral emboli and in many cases known causes of strokes.²¹ In 2 studies restricted to patients with cryptogenic strokes, DVTs were found in 3 of 23 (13%)²² and 1 of 14 (7%)²³ patients with PFOs. The latter 4 studies each used bilateral contrast venography, which may be less sensitive to DVTs in the pelvis as compared to other sites.^{24,25}

Pelvic veins may be an important and underappreciated source of thromboemboli. At autopsy, the pelvic veins were the only source of paradoxical emboli in 19 of 86 patients (22%) in whom sources could be found,^{26,27} and isolated pelvic DVTs were found in 16% of patients with pulmonary emboli.²⁸ Spritzer et al,²⁹ in 769 consecutive MRV studies of the entire leg and pelvis, found that DVTs isolated to the pelvic veins were more common than in the calf veins and almost as common as in the thigh veins. Other evaluation techniques may have reduced diagnostic sensitivity for pelvic DVTs.^{24,30} Two prior studies found MRV useful for the diagnosis of pelvic DVTs in patients with strokes and interatrial communication.^{31,32}

Calf veins may also be an important source of thromboemboli in the setting of cryptogenic stroke. Isolated calf vein DVTs are more common than DVTs in any other site following stroke^{17,33} and at autopsy.³⁴ Proximal propagation may occur in 20% to 28% of calf vein DVTs.^{35,36} Embolization can occur without propagation; for example, isolated calf DVTs were found at autopsy in 36% to 46% of patients with pulmonary embolisms.³⁷ In general medical practice, calf vein thrombi are associated with small emboli, any consequent pulmonary emboli tend to be small and asymptomatic, and these DVTs are therefore considered low risk for important pulmonary events.^{38,39} As a result, anticoagulation is initiated only if repeat testing shows proximal extension.⁴⁰ However, small thrombi that are associated with minor injuries to the lung might have important effects on reaching cerebral arteries with diameters of 1 mm.⁴¹ Therefore, the

response to an isolated calf vein DVT may need to be modified when there is significant risk for the transmission of embolic material to the cerebral arterial circulation.

Several features of the study generate caution when generalizing to all patients with cryptogenic strokes. Most patients in whom paradoxical embolisms were suspected (Table 1) had diagnoses suggesting hypercoagulable conditions, which are not likely the case in most stroke populations. This may have been due in part to the high rate of neoplastic diseases among patients seen at UW. In most cases, the sizes of the interatrial shunts were not measured. Such data might have provided greater insight into stroke pathogenesis in patients with and without DVTs. Moreover, the methods used to diagnosis the presence of interatrial shunts may not have been optimal for the most accurate measurement of shunt size.⁴²

The current study identified 10 patients whose cryptogenic strokes arose from paradoxical embolisms on possible or probable bases. Unlike reports for pulmonary embolism,³⁸⁻⁴⁰ isolated DVTs in the calf and pelvic veins accounted for 50% of all patients, supporting the utility of a broad assessment of subdiaphragmatic veins in the setting of cryptogenic strokes and interatrial shunts. Sensitivity for DVTs may be improved by use of more than one diagnostic technique. Prospective studies are needed to better define the true prevalence of subdiaphragmatic DVTs acutely after stroke.

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